REMARKS

Claims 1, 2, 4-11, 21, 26-28, and 30-33 are pending in this application. Claims 30-32 have been canceled. Claims 1, 7, 10, 11, 21, and 26-28 have been amended. No new matter has been added by these amendments. Reconsideration is respectfully requested in light of the following remarks and amendments.

I. Specification

The disclosure has been objected to because of the following informalities: on page 23 line 24, Figure 14 appears to be mistakenly referred to as Figure 4; and further on page 30, line 25, acetonitrile is misspelled.

Applicants have amended page 23, line 24, Figure 4 to read Figure 14. Support for this amendment is found throughout the specification and at page 23, line 24-26. No new matter has been added by this amendment.

Further, Applicants have amended page 30, line 25 to correct the typographical error referred to above. Support for this amendment is found throughout the specification and at page 30, line 25. No new matter has been added by this amendment.

II. Claim Rejections 35 U.S.C. 112, second paragraph

Claims 1-2, 4-11, 21, 26-28, and 31 are rejected under 35 U.S.C. 112, second paragraph as being indefinite for failing to point out and distinctly claim the subject matter which Applicant regards as the invention.

The Examiner suggests that Claims 1, 7, and 28 are vague and indefinite because the term "substantial separation" is a relative one and not defined by the claim and the specification does not provide a standard for ascertaining the requisite degree. Applicants respectfully disagree. However, in an earnest attempt to facilitate prosecution of this application, claims 1, 7, and 28 have been amended to recite to remove the term substantial. Support for this amendment is found throughout the specification.

The Examiner further suggests that claims 1, 7, 10, 11, 27-28 and 31 are vague and indefinite because the term "substantially free" is a relative one and not defined by the claim and the specification does not provide a standard for ascertaining the requisite degree. Applicants respectfully disagree. However, in an earnest attempt to facilitate prosecution of this application, claims 1, 7, 10, 11 and 27-28

have been amended to remove the term substantially. Claim 31 has been canceled.

The Examiner suggests that claims 7, 10 and 26 are vague and indefinite as the term "substantially denatured" is a relative term which is not defined by the claims and that the specification does not provide a standard for ascertaining the requisite degree. Applicants respectfully disagree. However, in an earnest attempt to facilitate prosecution of this application, claims 7,10 and 26 have been amended to remove the term "substantially".

The Examiner further suggests that claim 20 recites the limitation "method". Applicants believe that the Examiner intended to recite claim 21 as having the limitation "method", as Claim 21 is dependent on claim 20, which was previously canceled. The Examiner further suggests that there is insufficient antecedent basis for the limitation in the claim.

Claim 21 has been amended to depend on claim 1, and now sets forth the proper antecedent basis.

The Examiner yet further suggests that claims 30-32 are vague and indefinite because the term "stabilized" is a relative one and not defined by the claim and the specification does not

provide a standard for ascertaining the requisite degree. Applicants respectfully disagree.

The term stabilized is defined as being free of an agent capable of catalyzing RNA degradation, and is supported throughout the specification, and specifically at page 30, lines 26-29. By definition, an RNA molecule is stable if there is nothing present to catalyze its degradation. The present invention specifically removes these catalysts. Applicants respectfully request reconsideration and withdrawal of this rejection.

In light of the aforementioned remarks and amendments, it is respectfully requested that these rejections under 35 U.S.C. 112 be withdrawn.

III. Claim Rejections 35 U.S.C. 102

A. Gjerde (WO 98/56798 and US 5,972,222)

Claims 1-2, 4-6, 11, 21, 26, 27, and 30-33 are rejected under 35 U.S.C. 102(e) as being anticipated by Gjerde (WO 98/56798). Claims 1-2, 4-6, 11, 21, 26, 27, and 30-33 are further rejected under 35 U.S.C. 102(e) and 35 U.S.C. 102 (a), as being anticipated by Gjerde (US 5,972,222).

The Examiner suggests that Gjerde (WO 98/56798) teach separation of polynucleotide by MIPC wherein multivalent cations are removed from all aspects. The separation media of Gjerde (WO 98/56798) can be silica, and support non-polar organic polymers or long chain C1 to C24 hydrocarbon groups bound to inorganic substrate. This separation media is taught to have an average diameter of 1-100 microns. The Examiner suggests that media can be used in the separation of RNA, although for the purposes of description, DNA is described, and that this procedure can be used for batch process. The Examiner further suggests that the method taught comprises contacting the separation media with eluting solution A, which consists of 0.1 M TEAA pH 7.2 and solution B, which consists of 0.1 M TEAA and 25% acetonitrile. The Examiner suggests that procedure disclosed by Gjerde (WO 98/56798) is the same as that recited in the instant claims, and taught in the instant specification, and it would reasonably be expected to yield RNA that is substantially free of agents capable of catalyzing degradation of RNA.

Further, the Examiner suggests that Gjerde (US 5,972,222) teach the separation of polynucleotides by MIPC, wherein multivalent cations are removed from all aspects. The separation media of Gjerde (US 5,972,222) can be silica, and support non-

polar organic polymers or long chain C1 to C24 hydrocarbon groups bound to inorganic substrate. This separation media is taught to have an average diameter of 1-100 microns. The Examiner suggests that Gjerde (US 5,972,222) can be used in the separation of RNA, although for the purposes of description, DNA is described, and that this procedure can be used for batch process. The Examiner further suggests that the method taught by Gjerde (US 5,972,222) comprises contacting the separation media with eluting solution A, which consists of 0.1 M TEAA pH 7.2 and solution B, which consists of 0.1 M TEAA and 25% acetonitrile. The Examiner suggests that procedure disclosed by Gjerde (US 5,972,222) is the same as that recited in the instant claims, and taught in the instant specification, and it would reasonably be expected to yield RNA that is substantially free of agents capable of catalyzing degradation of RNA.

Applicants respectfully disagree.

First, it is respectfully pointed out that the application for the present invention describes MIPC processes via incorporation by reference of co-pending and commonly assigned U.S Patent Application No. 5,972,222. U.S Patent Application No. 5, 972,222 and PCT application WO 98/56798 are related filings, each of which claim priority from commonly assigned provisional

applications Serial No. 60/049,123 and Serial No. 60/063,835. As such the subject matter of these applications is considered to be set forth in its entirety in the Detailed Description of the present invention.

The present invention further teaches automated options for sample selection, mobile phase gradient selection and control, column and mobile phase temperature control and fraction collection, as set forth throughout the specification and particularly at pages 12 through 16.

In an earnest effort to further distinguish the claimed subject matter from the recited applications and facilitate prosecution and allowance, claim 1 have been amended to clarify that in claimed method the flow of the organic solvent present in the mobile phase is controlled by a mobile phase flow control means which is responsive to computer control, as supported at page 12 at lines 25-31. Neither U.S. Patent Application No. 5,972,222 nor PCT application WO 98/56798 disclose the advantages of such mobile phase flow control means which are responsive to computer control.

Withdrawal of this rejection is respectfully requested.

B. Oefner US 6,453,244.

Claims 1-2, 4, 6-10, 21, and 30-33 are rejected under 35 U.S.C. 102(a), as being anticipated by Oefner (US 6,453,244).

The Examiner suggests that Oefner teaches elution of RNA with a mobile phase containing an ion-pairing reagent and organic solvent under denaturing conditions such as heat or chemicals. The solid support is comprised of silica and the mobile phase is comprised of TEAA and acetonitrile. Denaturing conditions include temperatures up to 70°C. The separation media has an average diameter of 1-100 microns, the concentration of TEAA is about 0.05 to 1.0 Molar and about 25% acetonitrile. The Examiner also suggests that this invention can be used in the separation of RNA and the procedure can be used for large numbers of samples to be analyzed. The Examiner further suggests that procedure disclosed by Oefner is the same as that recited in the instant claims, and taught in the instant specification, and it would reasonably be expected to yield RNA that is substantially free of agents capable of catalyzing degradation of RNA.

Applicants respectfully disagree.

Claim 1 has been amended to recite that the separation of the RNA molecule from the agent capable of catalyzing the degradation of RNA using Matched Ion Polynucleotide Chromatography, support for

this amendment is found throughout the specification and at claim 5 as filed. The present invention teaches the use of MIPC and does not require a separate pretreatment denaturing step. The present invention is particularly useful for determining RNA molecules having lengths exceeding 100 nucleotides, and is especially useful with molecules over 200 nucleotides. The present invention is also capable of determining of up to 20,000 nucleotides (specification p.26, lines 14-24). The stabilized RNA of the present invention is capable of being stored at room temperature for up to seven days with no degradation.

In contrast, Oefner teaches a two step method for detecting polymorphisms by denaturing high performance liquid chromatography (HPLC). The first step is a required pretreatment in which the nucleic acids are completely denatured via heat or chemicals. In the second step, the pretreated nucleic acids are put through HPLC, under further denaturing conditions (Abstract, Column 3, lines 26-32). The methods taught by Oefner, oligomers are useful for determining nucleotides of a shorter length, i.e. preferably less than 100 nucleotides long (Column 7, lines 59-64) and more preferably oligomers of 40-90 nucleotides (Column 13, lines 47-50). Oefner does not teach or suggestion that the RNA molecules resulting from their methods are stable, nor does

Oefner teach MIPC techniques, nor that said molecules could remain stable.

MPEP 2131 states that "a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. Thus, Oefner can not be found to teach or anticipate the present invention, as it does not teach all of the limitations of the invention.

Withdrawal of this rejection is respectfully requested.

C. Joachimiak

Claims 1-2, 4, 6-10, 21, and 30-33 are rejected under 35 U.S.C. 102 (b), as being anticipated by Joachimiak (ABRF News December 1992).

The Examiner suggests that Joachimiak teaches large scale purification of RNA on columns using non-polar silica separation medium. For separation, silica gels are used in the presence of ion-pairing reagent and organic solvent such as 0.1 M TEAA in an acetonitrile gradient. Denaturing conditions include temperatures up to 60°C or 7M urea or high pH. The Examiner further suggests that procedure disclosed by Joachimiak is the same as that recited in the instant claims, and taught in the instant

specification, and it would reasonably be expected to yield RNA that is substantially free of agents capable of catalyzing degradation of RNA.

Applicants respectfully disagree.

The Joachimiak reference provides a review and summary of known methods for purifying synthetic oligoribonucleotides. The methods that are taught are all well known and practiced in the art during 1992. To clarify the present invention, claim 1 has been amended to recite that the separation of the RNA molecule from the agent capable of catalyzing the degradation of RNA using Matched Ion Polynucleotide Chromatography, support for this amendment is found throughout the specification and at claim 5 as filed. It has been indicated that the limitation of claim 5 is allowable in view of the Joachimiak reference.

Withdrawal of this rejection is respectfully requested.

D. Bonham and Danielpour (Biotechniques vol. 21, 1996)

Claims 30-32 are rejected under 35 U.S.C. 102 (b), as being anticipated by Bonham and Danielpour (Biotechniques vol. 21, 1996).

The Examiner suggests that Bonham and Danielpour teach an isolation of RNA which is stable and the resulting sample is devoid of RNASE inhibitors as claimed by the present invention.

Applicants respectfully disagree.

Bonham and Danielpour teach a method of improving the results of a commercially available kit used for RNA isolation. Bonham and Danielpour do not teach a stabilized solution devoid of RNASE inhibitors which maintain stability for long periods of time. However, in an earnest attempt to facilitate prosecution of this case, Applicants have canceled claims 30-32. Applicants reserve the right to pursue such canceled subject matter in a continuing or divisional application at a later time.

It is therefore respectfully requested that this rejection under 35 U.S.C. 102 be withdrawn.

Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly,

favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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